Applicant's have amended claim 1 by inserting the phrase - wherein said composition is optimal for treating HCV infection in said human, -- to further clarify the scope of the composition.

Applicant's have amended claim 2 by inserting the phrase - wherein said method is optimal for treating HCV infection in said human, -- to further clarify the scope of the method.

Applicant's have amended claim 5, to depend from claims 2-4, thereby removing improper dependency from multiply dependent claim 5.

Applicant's have amended claim 11 to depend from claim 9, thereby removing improper dependency from claim 10.

Applicant's have amended claim 12 to depend from claim 9, thereby removing improper dependency from claim 10.

None of the above amendments add any new matter. These amendments are further discussed below in the context of the Examiners rejections.

THE OBJECTION

The Examiner has objected to claims 8-12 as being in improper form because a multiple dependent claim may not refer to another multiple dependent claim. Specifically, the Examiner asserts multiply dependent claim 8 depends from multiply dependent claim 5.

As noted above, applicants have amended claim 8 to depend only from claim 7 thus obviating this rejection.

Additionally, applicants have amended method claim 5 to depend only from method claims 2-4.

Applicants now believe claims 5 and 8 are in sufficient condition for allowance.

THE REJECTIONS

I. 35 U.S.C. § 102(b)

1) Claims 1-2 and 5-10 stand rejected under 35 U.S.C. § 102(b) as being anticipated by P. Glue in *Seminars in Liver Disease*, Vol. **19**, supp. 1, pp.17-24 (1999) (hereinafter "Glue"; copy enclosed, see, Exhibit 1). Specifically, the Examiner contends that Glue teaches coadministration of interferon alpha and ribavirin to treat Hepatitis C at a dosage of 600mg twice daily, and that this same dose is described by applicants at specification page 14, line 33 and at specification page 16, Table 2. The Examiner further asserts that the dose disclosed by Glue "anticipates claims drawn to compositions and methods using levels determined by applicant's method." Applicants traverse.

In Glue, healthy volunteers and patient populations were administered Ribavirin **alone**. In Glue, a 600mg dose of Ribavirin was given either once or twice daily in healthy volunteers and patients. Ibid, p. 19. Thus, there is no disclosure in Glue that **co-administration** of alpha interferon with Ribavirin, in a dosage amount as determined by applicants' invention, would be useful for treating Hepatitis C.

For this reason, applicants believe that the composition of claim 1 is novel over Glue. For the same reason, the method of claim 2, also, is novel over Glue. Because claims 5-10 depend either directly or indirectly from claims 1 and 2, they, too, are novel over Glue. Consequently, applicants request that the Examiner

withdraw this 35 U.S.C. § 102(b) rejection of claims 1, 2, and 5-10.

2) Claims 1-2, 5-9, and 12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by T. Wright et al. in *Hepatology*, Vol. **3**,(4), p. 408A (1999) (hereinafter "Wright", copy enclosed, see, Exhibit 2). The Examiner asserts that Wright teaches the use of VX-497 to treat hepatitis C at the dose determined by applicant on p. 17 to be optimal and teaches its co-administration with interferon alpha. The Examiner further asserts that "a new means of determining a dose already known does not render the dose itself novel." Applicants traverse.

Wright describes a 28 day double blind, placebo controlled study of VX-497 **alone** at three dose levels in 30 interferon non-responsive adult patients with active Hepatitis C. The study does not include any combination therapy using VX-497 and interferon. Applicants have specifically disclosed two dose levels of VX-497 (100 mg q 8 hrs and 300 mg q 8 hrs) **in combination** with 3 MU of IFN alpha 2b tiw. Therefore, Wright does not anticipate applicants' composition of claim 1 and the methods of claims 2, 5-9. Accordingly, applicants request that the Examiner withdraw this 35 U.S.C. § 102(b) rejection.

II. 35 U.S.C. § 103(a)

Claims 1, 2, 5-9, and 12 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over M. Brunet et al. in *Transplantation Int.*, Vol. **13** suppl. 1, pp. S301-S305 (2000) (hereinafter "Brunet"; copy enclosed, see, Exhibit 3) in view of W. Markland et al., in

Antimicrobial Agents and Chemotherapy, Vol. **44** (4), pp. 859-866 (2000) (hereinafter "Markland"; copy enclosed, see, Exhibit 4). Specifically, the Examiner asserts that Markland teaches that an IMPDH inhibitor, such as mycophenolic acid (MPA), in combination with interferon alpha, would be useful for treating Hepatitis C. Further, the Examiner asserts that Brunet teaches the 0.5-1.0 gram b.i.d. dose for MPA claimed by applicants. The Examiner further asserts that "it would have been *prima facie* obvious to one of ordinary skill in the art to combine the teachings of Markland et al. with those of Brunet et al. to administer 0.5-1.0 grams of mycophenolic acid twice a day in combination with interferon alpha to treat hepatitis C." Applicants traverse.

Applicants' invention does not merely provide fixed dosage levels applicable to all Hepatitis C patients. In contrast, applicants' invention provides a method for determining a dosage level that is **optimal** for a patient.

In fact, Brunet highlights the individual variability in the response to IMPDH inhibitors within patients, and thus underscores the need for optimizing the dosage levels for Hepatitis C patients. Brunet concludes that:

> "Concerning inhibition of IMPDH activity, a considerable interindividual variability could be observed. Patients with similar plasma MPA predose concentrations, and also with comparable MPA-AUC_{0-12} values have different degrees of IMPDH inhibition. **These findings suggest the important role that Pharmacodynamic monitoring could play in the improvement of individual immunosuppressive therapy.**" [Emphasis added.]

It is well known in the art that a given dosage level will generate different Cmin and Cavg ratios for every Hepatitis C patient treated based on a variety of well established pharmacokinetic parameters. See e.g., Ene Ette *et al.*, "Population Pharmacokinetic Modeling: The Importance of Informative Graphics", *Pharmaceutical Research*, **12**(12), p. 1845-1855 (1995) (copy enclosed, see, Exhibit 5). See, also "Guidance for Industry: Population Pharmacokinetics," published by the United States Food and Drug Administration, Washington D.C. (1999) (copy enclosed, see, Exhibit 2).

Thus, neither Brunet nor Markland suggest the optimal dosage of claim 1. And, the method of treating a patient with such an optimal dosage (claim 2) is neither taught nor even suggested by Brunet and Markland. Applicants' invention provides methods and compositions that are optimized for each patient's pharmacokinetic profile by factoring into the dosage level the Cmin and Cavg ratios for every Hepatitis C patient. This is the key feature of applicants' invention. For this reason, Brunet in combination with Markland does not render obvious claims 1, 2, 5-9 and 12. Accordingly, applicants request that the Examiner withdraw this § 103 rejection.

III. 35 U.S.C. § 112, first paragraph

Claims 3, 4, and 5-12 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of skill in the art to make or use the invention. Specifically, the Examiner asserts that in applicants' specification "[W]hat is provided are results for higher doses already known to be effective.

Thus, there are no working examples presented and no other guidance provided that would allow one of skill to predict that these lower levels would be useful." Applicants traverse.

The Examiner's analysis of the enablement requirement focuses on the dosage level. But, that focus is misplaced.

Applicants' invention does not relate to a specific range of dosage levels. On the contrary, the claimed methods relate to an optimal ratio of Cavg/Cmin. See, specification page 7, lines 6-9:

> "The present invention provides a band of IMPDH inhibitor concentrations, wherein the lower end of the band is defined by the ratio Cavg/Cmin being 1, and the upper end of the band is defined by that ratio being 10."

Thus, any enablement inquiry should, properly and solely, focus on whether the claimed methods, as drawn to various ratios Cavg/Cmin, are sufficiently exemplified so as to provide the requisite assurance to one of skill in the art that the claimed methods have the asserted utility.

Applicants have exemplified optimal compositions comprising alpha-interferon 2b and ribavirin (see, Example 1, specification page 13). Applicants have exemplified therein *inter alia* a ribavirin dosage of 600 mg BID provides a Cavg of 19000 ng/ml and a Cmin of 2250 ng/ml (see, Table 1, specification page 16), thus providing a Cavg/Cmin ratio of 8.44.

Applicants have exemplified optimal compositions comprising alpha interferon 2b and VX-497 (see, Example 2, specification page 17). Applicants have

exemplified therein *inter alia* a VX-497 dosage of 300 mg TID and 100 mg TID, resulting in a Cavg of 1107 ng/ml and 520 ng/ml, respectively, and a Cmin of 250 ng/ml, and 168 ng/ml, respectively for the two dosage levels (Table 2 specification page 18). The resulting Cavg/Cmin ratios are 4.42 and 3.09, respectively for the two dosage levels.

Applicants have exemplified optimal composition comprising alpha interferon 2b and mycophenolate (see, Example 3, specification page 20). Applicants have exemplified therein *inter alia* a mycophenolate dosage of 1000 mg BID, resulting in a Cavg of 3869 ng/ml, and a Cmin of 2060 ng/ml (see, Table 3, specification page 21). The resulting Cavg/Cmin ratio is 1.87.

Thus, as set forth above, applicants have exemplified Cavg/Cmin ratios of 8.44 (Table 1), 4.42 and 3.09 (Table 2) and 1.87 (Table 3). In each instance, a significant drop in %HCV RNA was observed. And, pertinent to the enablement requirement, applicants' exemplification spans the Cavg/Cmin ratios of 1-10. Therefore, applicants' specification does provide the requisite assurance that the claimed methods have the asserted utility. To require more would unduly burden applicants to provide an enablement beyond the threshold mandated by § 112, first paragraph. For this reason, applicants request that the Examiner withdraw this § 112, first paragraph rejection.

IV. 35 U.S.C. § 112, second paragraph

Claims 8-12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Examiner asserts that "one of skill in the art would not

be able to determine the limitations Applicant intended claims 8-12 to encompass."

Applicants have obviated this rejection by amending claim 8 to delete the phrase "any of claims 1-7" and replace therefor "claim 7" thereby providing a proper antecedent basis for claim 8.

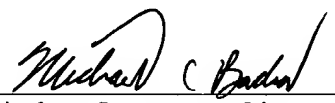
Applicants have also amended claims 11 and 12 to depend solely from claim 9. Claims 11 and 12, as amended, have a proper antecedent basis.

For the reasons set forth above, applicants request that the Examiner withdraw his 35 U.S.C. § 112, second paragraph rejections.

CONCLUSION

Applicants request that the Examiner enter the above amendments, consider the accompanying remarks, and allow the pending claims to pass to issue.

Respectfully submitted,



Michael C. Badia
Reg. No. 51,424
Agent for Applicants
Nandakumar Govindaswamy
Ltd. Recognition
Attorney for Applicants

Vertex Pharmaceuticals Incorporated
130 Waverly Street
Cambridge, MA 02139-4242
Tel.: (617)444-6467
Fax.: (617)444-6483

APPENDIX 1

1. (Amended) A composition for treating HCV infection in a human, wherein said composition is optimal for treating HCV infection in said human, comprising alpha-interferon or a derivative thereof and an IMPDH inhibitor, wherein said IMPDH inhibitor is present in said composition in an amount such that a ratio of Cavg/Cmin is between 1 to 10;

wherein:

Cavg is average plasma concentration produced by said IMPDH inhibitor in said human; and

Cmin is estimated trough concentration produced by said IMPDH inhibitor in said human.

2. (Amended) A method for treating HCV infection in a human, wherein said method is optimal for treating HCV infection in said human, comprising the step of administering to said human an optimal composition comprising alpha-interferon or a derivative thereof and an IMPDH inhibitor, wherein said optimal composition contains said IMPDH inhibitor in an amount such that a ratio of Cavg/Cmin is between 1 to 10;

wherein:

Cavg is average plasma concentration produced by said IMPDH inhibitor in said human; and

Cmin is estimated trough concentration produced by said IMPDH inhibitor in said human.

5. (Amended) The method according to any of claims [1-4] 2-4, wherein said ratio is between 1-8.

8. (Amended) The method according to [any of claims 1-7] claim 7, wherein said IMPDH inhibitor is selected from mycophenolic acid, ribavirin, VX-497, VX-148 or VX-944.

11. (Amended) The method according to claim [10] 9, wherein said IMPDH inhibitor is VX-497.

12. (Amended) The method according to claim [10] 9, wherein said IMPDH inhibitor is mycophenolic acid.

reservoirs via inhibition of the NAD+-dependent enzyme, inosine monophosphate dehydrogenase ("IMPDH"), which is the rate-limiting enzyme in the *de novo* nucleotide biosynthesis, has been identified as an attractive target for anti-HCV therapy. See, VX-497, *Drugs of the Future*, **25(8)**, pp. 809-814 (2000). Known inhibitors of IMPDH include Ribavirin, VX-497, mycophenolate mofetil (~~Cellcept™~~ CELLCEPT®), tiazofurin and mizoribine. Recently, a combination therapy, using alpha-interferon and Ribavirin™, has shown greater efficacy in treating HCV infection than a monotherapy using either entity. However, the combination therapy is not problem free. Alpha interferon is known to cause side effects such as high fevers, headaches, nausea and depression. Ribavirin tends to increase these side effects, and also cause haemolytic anaemia. Hepatologists are reluctant to reduce the dosage of Ribavirin below 800 mg/day (see, Foster, G. R. and Thomas, H. C., *Balliere's Clinical Gastroenterology*, **14(2)**, pp. 255-264 (2000). The minimum effective dose of Ribavirin is not yet known.

Thus, there is a need for a therapy that takes advantage of the synergy and/or additivity observed between alpha-interferon and an IMPDH inhibitor in the combination therapy, but preferably without the drawbacks associated with the individual components of the combination therapy.

Thus, there is a need for an optimal composition for treating HCV infection in a human, comprising alpha-interferon and an IMPDH inhibitor.

There is also a need for a method for treating HCV infection in a human comprising the step of administering to said human an optimal composition comprising alpha-interferon and an IMPDH inhibitor.

Table 1: Effects of Interferon alpha 2b (~~Intron-A~~ INTRON A®) and Ribavirin in HCV patients

Dose of Ribavirin	IC50ap (ng/mL)	IC50av (ng/mL)*	Cavg (ng/ml)	Cmin (ng/mL)	APQ	AAQ	FQ	HCV RNA drop
600 mg BID	976	11956	19000	2250	19.5	1.6	0.19	30%[a], 60%[b]
400 mg BID	976	11956	7083	1450	7.3	0.6	0.12	N/A
200 mg BID	976	11956	3542	740	3.6	0.3	0.06	N/A

*Micromolar IC50 of ribavirin in Table 1 converted to ng/mL using a molecular weight of 244.

** Estimated per the single dose kinetics reported by Glue, P, *Sem. Liver Dis.* 19: 17-24, and using the accumulation factor reported by Khakoo *et al. Br. J. Clin. Pharmacol.*, **46**, pp.563-570 (1998). Cavg is calculated from AUC(0-t)/dosing interval.

[†]Data for SR from McHutchison and Poynard (1999), see above.

[a]For genotype 1; [b]For non-genotype 1.

N/A: Not available

Table 2: Effects of Interferon alpha 2b (~~Intron A~~ INTRON A®) and VX-497 in naïve HCV patients

Dose of VX-497	IC50ap (ng/mL)	IC50av* (ng/mL)	Cavg** (ng/ml)	Cmin** (ng/mL)	APQ	AAQ	FQ	% HCV RNA drop
300 mg TID	45	140	1107	250	24.6	7.93	1.8	50%
100 mg TID	45	140	520	168	11.6	3.74	1.2	53%
100 mg BID	45	140	359	262	8	2.6	1.9	N/A
50 mg TID	45	140	266	116	5.9	1.9	0.83	N/A
50 mg BID	45	140	150	107	3.3	1.06	0.76	N/A

*Micromolar IC50 in Table 1 converted to ng/mL using the molecular weight of VX-497 as 452.

** Estimated assuming linearity and based upon expected steady-state concentrations and Cavg = AUC(0-t) / dosing interval

*** From VX-497-003 trial in genotype 1 naïve patients receiving ~~Intron A~~ INTRON A® with VX-497 for 4 weeks

N/A: Not available

EXAMPLE 3

A four-week analysis of the antiviral effects of the combination of pegylated IFN-2a (~~Pegasys~~ PEGASYS®) with the MTD of mycophenolate (as the mofetil ester, ~~CellCept~~ CELLCEPT® at 1000 mg BID) showed a lower proportion of patients achieving significant antiviral effects, when compared to a group receiving ~~Pegasys~~ PEGASYS® and RBV. However, when treated for six months with ~~Pegasys~~ PEGASYS® and ~~CellCept~~ CELLCEPT®, similar "end of treatment" antiviral efficacy was observed for MMF and ~~Pegasys~~ PEGASYS® as the combination of ribavirin and ~~Pegasys~~ PEGASYS®.

Once again, the AAQ for MMF is critical in determining the activity of MMF in combination with ~~Pegasys~~ PEGASYS® in hepatitis C patients. It is quite evident that the AAQ for all three dose levels of mycophenolate are well below 1. It is important to understand that in vitro inhibitory concentrations of MMF have not been predictive of in vivo EC50 for MMF. Numerous reasons for this phenomenon include rapid glucuronidation, and enterohepatic recirculation. Hence, a correction for APQ is obtained by dividing average plasma concentration by in vivo IC50.

In the case of mycophenolate, there is clear evidence of in vivo IMPDH inhibition requiring much higher concentrations. Therefore, the FQ is corrected for the loss of in vitro potency (a factor of 337.5). The AI is obtained by correcting the APQ for the fold change between antiproliferative to antiviral IC50 in vitro and an AI is obtained from the algorithm described. For mycophenolate, all three dose levels listed produce a ratio in the range of 1.9 to 2.5.

Hence, it is expected that mycophenolate at doses of 0.5 g to 1 g twice daily in combination with IFN and/or its pharmaceutical dosage forms (such as ~~PegIntron~~ PEGINTRON® and ~~Pegasys~~ PEGASYS®), will elicit an antiviral response in hepatitis C patients.

Table 3: Effects of Mycophenolate with pegylated IFN-2a (~~Pegasys~~ PEGASYS®) in HCV patients

Dose of MPA	IC50ap (ng/mL) *in vitro*	IC50ap** (ng/mL) *in vivo*	IC50av* (ng/mL)	Cavg*** (ng/mL)	Cmin** (ng/mL)	APQ	AAQ	FQ	% HCV RNA drop
1000 mg BID	32	10800	122	3869	2060	0.36	0.095	0.05	31[a], 72[b]
750 mg BID	32	10800	122	3425	1400	0.32	0.084	0.034	N/A
500 mg BID	32	10800	122	3163	1630	0.29	0.076	0.04	N/A

Micromolar IC50 of mycophenolate in Table 1 converted to ng/mL using a molecular weight of 320.

** Estimated from Brunet et al., Transpl Int 2000; 13 (Suppl 1): S301-S305

***Cavg obtained from median AUC(0-t)/dosing interval from Brunet *et al.*, Transpl. Int., **13**, pp. 301-305 (2000)

† In vivo IMPDH inhibition correction factor estimated as the ratio of in vivo IC50/in vitro IC50 for cellular proliferation (i.e. 10800/32 = 337.5)

††Data from Nezam Afdel and Steven K. Herrine (presented at DDW, 6/2001)

[a] For non-responders to ~~Rebetron~~ REBETRON® with 90% genotype 1 patients

[b] For relapsers on ~~Rebetron~~ with 79% genotype 1 patients REBETRON®

N/A: Not available

reservoirs via inhibition of the NAD+-dependent enzyme, inosine monophosphate dehydrogenase ("IMPDH"), which is the rate-limiting enzyme in the *de novo* nucleotide biosynthesis, has been identified as an attractive target for anti-HCV therapy. See, VX-497, *Drugs of the Future*, **25(8)**, pp. 809-814 (2000). Known inhibitors of IMPDH include Ribavirin, VX-497, mycophenolate mofetil (CELLCEPT®), tiazofurin and mizoribine. Recently, a combination therapy, using alpha-interferon and Ribavirin™, has shown greater efficacy in treating HCV infection than a monotherapy using either entity. However, the combination therapy is not problem free. Alpha interferon is known to cause side effects such as high fevers, headaches, nausea and depression. Ribavirin tends to increase these side effects, and also cause haemolytic anaemia. Hepatologists are reluctant to reduce the dosage of Ribavirin below 800 mg/day (see, Foster, G. R. and Thomas, H. C., *Balliere's Clinical Gastroenterology*, **14(2)**, pp. 255-264 (2000). The minimum effective dose of Ribavirin is not yet known.

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400 mg BID	976	11956	7083	1450	7.3	0.6	0.12	N/A
200 mg BID	976	11956	3542	740	3.6	0.3	0.06	N/A

*Micromolar IC50 of ribavirin in Table 1 converted to ng/mL using a molecular weight of 244.

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[†]Data for SR from McHutchison and Poynard (1999), see above.

[a]For genotype 1; [b]For non-genotype 1.

N/A: Not available

Table 2: Effects of Interferon alpha 2b (INTRON A®) and VX-497 in naïve HCV patients

Dose of VX-497	IC50ap (ng/mL)	IC50av* (ng/mL)	Cavg** (ng/ml)	Cmin** (ng/mL)	APQ	AAQ	FQ	% HCV RNA drop
300 mg TID	45	140	1107	250	24.6	7.93	1.8	50%
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100 mg BID	45	140	359	262	8	2.6	1.9	N/A
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** Estimated assuming linearity and based upon expected steady-state concentrations and Cavg = AUC(0-t) / dosing interval

*** From VX-497-003 trial in genotype 1 naïve patients receiving INTRON A® with VX-497 for 4 weeks

N/A: Not available

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A four-week analysis of the antiviral effects of the combination of pegylated IFN-2a (PEGASYS®) with the MTD of mycophenolate (as the mofetil ester, CELLCEPT® at 1000 mg BID) showed a lower proportion of patients achieving significant antiviral effects, when compared to a group receiving PEGASYS® and RBV. However, when treated for six months with PEGASYS® and CELLCEPT®, similar "end of treatment" antiviral efficacy was observed for MMF and PEGASYS® as the combination of ribavirin and PEGASYS®.

Once again, the AAQ for MMF is critical in determining the activity of MMF in combination with PEGASYS® in hepatitis C patients. It is quite evident that the AAQ for all three dose levels of mycophenolate are well below 1. It is important to understand that in vitro inhibitory concentrations of MMF have not been predictive of in vivo EC50 for MMF. Numerous reasons for this phenomenon include rapid glucuronidation, and enterohepatic recirculation. Hence, a correction for APQ is obtained by dividing average plasma concentration by in vivo IC50.

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that mycophenolate at doses of 0.5 g to 1 g twice daily in combination with IFN and/or its pharmaceutical dosage forms (such as PEGINTRON® and PEGASYS®), will elicit an antiviral response in hepatitis C patients.

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Micromolar IC50 of mycophenolate in Table 1 converted to ng/mL using a molecular weight of 320.

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